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Histological pattern of oesophageal tumours in Sudanese patients

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Dedication

To the soul of my Father.

To my Mother for her great help.

To my husband for his appreciated help.

To my Kids: Mazin , Hind and Ahmed.

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I would like to express my thanks and deepest gratitude and appreciation to my supervisor Dr. Ahmed Ibrahim Shumo for his generous advice encouragement and cooperation through this Study.

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Abbreviations:

Abbreviation	Meaning
CCL cell	Centrocyte-like cells
CD	Cluster of differentiation
CT	Computed tomography
DNA	Deoxy ribonucleic acid
GERD	Gastroesophageal reflux disease
GISTs	Gastrointestinal stromal cells
HPV	Human papilloma virus
IUCC	International union against cancer
MALT	Mucosa associated lymphoid tissue
MCV	Mean corpuscular volume
MRI	Magnetic resonance imaging
OSCC	Oesophageal squamous cell carcinoma
RNA	Ribonucleic acid
RR	Relative risk
SCC	Squamous cell carcinoma
TNM	Tumour node metastasis
VIP	Vasoactive intestinal polypeptide
WDHA.	Watery diarrhoea, hypokalaemia, achlorohydria synd.
WHO	World health organization

Abstract

Oesophageal tumours are either benign or malignant. Benign tumours are mostly mesenchymal in origin. With rare exceptions, malignant oesophageal tumours arise from the epithelial layer.

This is a retrospective study conducted in Sudanese patients at Ibn Sina hospital and NHL. The aim of the study is to determine histopathological pattern, age and sex distribution of oesophageal tumours.

The study comprised 102 patients of which 44 were males and 58 were females with a male to female ratio of 1:1.3. The age of all patients ranged between 29 – 90 with a mean of 65 years.

In this study no benign tumour was identified and all the cases were malignant tumours the histology of which was SCC and adenocarcinoma. The SCC being predominant comprising 89.1 %, with a male to female ratio of 1:1.6. There is striking male predominance in adenocarcinoma (10:1)

By revising the slides: 85 were SCC (83 %) , 4 basoloid squamous cell carcinoma (4%), 2 spindle cell carcinoma (2 %), 9 adenocarcinoma (9%), 1 case papillary carcinoma (1 %) , one case signet ring cell carcinoma and 1 anaplastic carcinoma (1%).

Invasive SCC represented the majority of cases (88%) while only 12% were intraepithelial.

In conclusion benign tumours and other tumours like carcinoid, lymphomas etc are rare. SCC is the most common oesophageal cancer in Sudanese patients as it is the case worldwide. Intraepithelial neoplasia is under diagnosed and this raises the importance of screening programs.

ملخص الأطروحة

تنقسم أورام المرئ الي أورام حميدة و أورام خبيثة. تنمو معظم الأورام الحميدة من النسيج الأوسط. بينما تنمو معظم الأورام الخبيثة من الخلايا المبطنة للغشاء الداخلى للمرئ . هذه الدراسة الى الوراء عن أورام المرئ فى المرضى السودانيين. أجريت فى مستشفى ابن سيناء والمعمل القومى الصحى بالخرطوم . تهدف الدراسة الى بحث التغيرات المرضية في الأنسجة ومعرفة توزيع المرض فى الأعمار المختلفة و علاقة نوع المرض مع الجنس.

تضمنت الدراسة 102 مريض منهم 44 من الرجال و 58 من النساء. نسبة المرضى من الرجال الى النساء 1.3:1 وتراوحت الأعمار بين 29-90 سنة و متوسط الأعمار 65 سنة.

لم تصادف هذه الدراسة اى حالة ورم حميد، وكانت الحالات أورام خبيثة اما ناشئة من الخلايا المبطنة للغشاء الداخلى للمرئ وهى تمثل 89.1 % وتوزيع المرض شبه متماثل فى الجنسين. أو سرطان غددى و هنا نسبة الرجال تفوق نسبة النساء فى الاصابة (1:10).

بالرجوع الى الشرائح وجدت 85 حالة سرطان ناشئ من الخلايا المبطنة للغشاء الداخلى للمرئ (83%) ، 4 حالات سرطان قاعدى (4%) ، حالتان سرطان مغزلى (2%)، 9 حالات سرطان غددى (9%)، حالة واحدة سرطان خاتمى (1%)، حالة واحدة سرطان حليمى (1%)، و حالة واحدة سرطان متحول أو ارتدادى (1%). 88% من حالات السرطان الناشئ من الخلايا المبطنة للغشاء الداخلى للمرئ كان سرطان متغلغل و 12% غير متغلغل.

خلصت الدراسة الى أن الأورام الحمبدة و بعض الأورام الخبيثة فى المرئ نادرة الحدوث. وأن النوع الأكثر انتشارا بين المرضى السودانيين هو السرطان الناشئ من الخلايا المبطنة للغشاء الداخلى للمرئ كما هو الحال فى غالب بلدان العالم. و أن معظم الالحالات التى تم

تشخيصها حالات متقدمة (سرطان متغلغل). و أشارت الدراسة الى أهمية الفحص الطبى الدورى خاصة للأعمار التى يكثر فيها حدوث المرض.

Chapter 1

(1) Introduction:

Benign tumors of the oesophagus are over shadowed by cancer of the esophagus. However, they can be a cause of morbidity and can lead to dysphagia and thoracic pain. The frequency of leiomyomas which are the most common benign tumors of the esophagus has been found to be almost 8% (1). Carcinomas of the esophagus raised a considerable medical and public health challenge in many parts of the world. Morphologically and etiologically two major types are distinguished, squamous cell carcinoma and adenocarcinoma (2). Worldwide, squamous cell carcinoma (SCC) constitutes 90% of esophageal cancers but in the United States there has been an exceptional increase in the incidence of adenocarcinomas associated with Barrett esophagus (3). Analysis of incidence rates by subsite and subtype showed an increase in adenocarcinomas of the oesophagus and gastric cardia, largely restricted to males. In females, the rise in incidence of squamous cell carcinoma of the oesophagus appeared to be more marked than the rise in adenocarcinomas (4). Most cases of oesophageal carcinomas occur in adults older than the age of 50 with a male to female ratio of 3:1. There are striking and puzzling differences in the geographic incidence of esophageal carcinoma. In the United States, there are about 6 new cases per 100,000 population per year, accounting for 1% to 2% of all cancer deaths. In regions of Asia extending from the Northern Provinces of China to the Caspian Littoral in Iran, the prevalence is well over 100 per 100,000, and 20% of cancer deaths are caused by oesophageal cancer (mainly squamous cell type), with females being affected

more often than males. These epidemiologic contrasts must contain causative clues that remain to be deciphered (3). The incidence in the Sudan is 1.4% of all malignant tumours. The disease affected both sexes equally; is most common at the age of 50-69 and is commoner in patients from the North. (5).

The risk factors for squamous cell carcinomas of the esophagus include esophageal disorders like longstanding esophagitis, achalasia, and Plummer Vinson syndrome. Smoking and alcohol are two important and well known risk factors. However, different influences must underline the very high incidence of this tumor among Moslems of Iran, who neither drink nor smoke. Dietary factors like deficiency of vitamins and trace metals, fungal contamination of food stuffs and high content of nitrites, nitrosamine are invoked. Strong association with human papilloma virus is noted in high incidence areas (3). It is suggested that ethnicity may influence esophageal cancer histology or ethnic background may place an individual at increased risk for certain types of esophageal cancer (6).The role of genetic predisposition is extremely ill-defined but the rare genetic syndrome of tylosis (hyperkeratosis of palms and soles) carries an almost certain probability of the development of esophageal cancer. Barret esophagus is the only recognized precursor of esophageal adenocarcinoma (3).

Esophageal lesions evoke a similar and remarkably limited range of symptoms. All produce dysphagia which is attributed either to deranged esophageal motor function or obstruction of the lumen (3).

Exfoliative cytology in experienced hands is an extremely accurate technique for the evaluation of esophageal lesions

particularly those of the lower third. For many years, it was clearly superior to radiography or endoscopy. However, since the introduction of the flexible fiberoptic endoscope, the diagnostic accuracy of direct-vision biopsy has become as high as that of cytology (1).

Only a small number of genotypes have been obtained on carcinomas of the esophagus, and most of these have been incomplete. Of the genes known to be altered in SCC of the esophagus, TP53 is most often found to be abnormal. The contribution of molecular studies to the prognosis of SCC of the esophagus is not yet firmly established (7).

Radiation therapy is the most common form of treatment for carcinomas of the upper two thirds of the esophagus and surgery (in the form of oesophagastrectomy) is usually performed for carcinoma of the lower third. Some authors advocated a combination of chemotherapy and radiation therapy, with or without surgery. In inoperable cases considerable palliation can still be achieved by well-planned irradiation (1).

Despite progress in therapy, carcinomas of the esophagus remain a tumor with somber prognosis. Patients often present with relatively advanced tumor because the tumor remains asymptomatic for a long interval. Progression of squamous cell carcinomas of the esophagus has been recorded to take 3 to 4 years (7).

Literature review

(1) Anatomy and physiology of the esophagus:-

The esophagus is a muscular tube, about 25 cm (10 in) long connecting the pharynx to the stomach. It begins in the neck at the caudal border of the cricoid cartilage. It pierces the diaphragm at the level of the tenth thoracic vertebra, and ends at the cardiac orifice of the stomach at the level of the eleventh thoracic vertebra.

Thus the esophagus is divided into cervical part, thoracic part and abdominal part. Arteries supplying the esophagus are derived from the inferior thyroid branch of the thyrocervical trunk, form the descending thoracic aorta, from the bronchial arteries, from the left gastric branch of the celiac artery, and from the left inferior phrenic branch of the abdominal aorta. The veins drain into the inferior thyroid veins, the azygos, hemiazygos and accessory hemiazygos veins. The abdominal part drains partly into the azygos vein and partly into the left gastric vein. The latter vein being a tributary of the portal vein. The lymph vessels from the upper third of the esophagus drains into the cervical nodes, the middle third into the paraeosophageal and paratracheal mediastinal nodes, and the lower third into the nodes around the aorta and celiac axis.The nerve supply is derived from the vagus and cervical sympathetic trunks (8).

Physiologically the oesophagus normally exhibits two types of peristaltic movements: primary peristalsis and secondary peristalsis. Primary peristalsis is simply a continuation of swallowing. This wave passes all the way from the pharynx to the stomach in about 8 to 10 seconds. If the primary wave fails to move all the food that has entered the esophagus into the

stomach, secondary peristaltic waves result from distension of the esophagus by the retained food, and they continue until all the food has emptied into the stomach. These secondary waves are initiated partly by intrinsic neural circuits in the esophageal myenteric nervous system and partly by reflexes that are transmitted through vagal afferent fibers from the esophagus to the medulla and then back again to the esophagus through vagal efferent fibers. To prevent reflux of stomach contents into the esophagus the esophageal circular muscle functions as a lower esophageal sphincter or gastroesophageal sphincter at the lower end of the esophagus. Anatomically, this sphincter is no different from the remainder of the esophagus. Physiologically, it normally remains tonically constricted (with an intra-luminal pressure at this point in the esophagus of about 30 mm Hg), in contrast to the mid portion of the oesophagus between the upper and lower sphincters, which normally remains relaxed. Another factor that prevents reflux is a valve-like mechanism of that short portion of the esophagus that lies immediately beneath the diaphragm before reaching the stomach (9).

(2) Histology of the esophagus:-

The histological structure of the esophagus follows the same general pattern as the rest of the alimentary tract:-

1. **The fibrous layer (serosa):-**

   It consists of an external adventitia of irregular, dense connective tissues containing many elastin fibers. Its fibers also penetrate and surround the fasciculi of muscle in the deeper layers.

2. **The muscularis externa:-**

It is 0.5-2.0 mm in thickness and consists of outer longitudinal and inner circumferential layers of muscle fibres. In the initial portion of the esophagus, both layers are striated muscle. In its middle third, smooth muscle fibres begin to appear deep to the striated muscle, and in the lower third, both layers of the muscularis consist entirely of smooth muscle.

3. The submucosa:-

It is 400-600 μm in thickness and contains interlacing bundles of collagen fibres, abundant elastic fibres, and many small blood vessels. The mucosa and sub mucosa, in the un-distended esophagus, form broad longitudinal folds that give the lumen a highly irregular outline.

4. The mucosa:-

The esophageal mucosa is 300-500 μm thick and has an epithelium that is a continuation of the stratified squamous epithelium lining the oropharynx. Stratum germinativum, stratum spinosum, and stratum corneum are identifiable, but the thickness and degree of keratinization of the stratum corneum vary greatly from species to species. The superficial cells retain their nucleus and have a few keratohyalin granules in their cytoplasm but show little evidence of heavy keratinization. Cells of the stratum spinosum have short microplicae that project into the intercellular spaces, and the processes of neighboring cells are attached by prominent desmosomes. In addition to their organelles, these cells contain bundles of intermediate filaments and 120-150 nm vesicles that contain eccentrically placed dense material. The base of the epithelium is quite irregular with closely spaced deep recesses in its under surface, occupied by papillae of the lamina propria. The cells of the stratum

germinativum are cuboidal and have desmosomes on their interdiagitating lateral surfaces and hemidemosomes at their base.

The intercellular spaces of the stratum corneum and outer portion of the stratum spinosum contain material that gives a strong staining reaction with Alcian blue at pH2.5 and is deeply stained with the periodic-acid-Schiff reaction for glyconjugates.

5. Oesophageal glands:-

Two kinds of esophageal glands are distinguished on the basis of their location. (1)The superficial mucosal glands are limited to the lamina propria and are found in limited number in the upper oesophagus and near its junction with the stomach. They are tortuous tubular glands lines with cuboidal or columnar epithelial cells that resemble those of the cardiac glands of the stomach. Owing to this resemblance, these glands are sometimes called cardiac esophageal glands. They are few in number and are interpreted by some as islands of ectopic gastric mucosa. Their small ducts join a larger duct that usually opens at the tip of a small papilla. (2) The submucosal glands are more widespread and extend into the submucosa.They are tubuloacinar glands arranged in small lobules that are drained by a single duct. The acini are made up of plump cells with their nucleus compressed to the base by droplets of mucus that occupy most of the cell volume. A second cell type is cuboidal with a centrally placed nucleus, a basophilic cytoplasm, and somewhat smaller and denser secretory droplets or granules. These cells are considered by some to be an earlier stage in the secretory cycle of the mucous cell, but others regard them as a separate serous cell type.

Like the minor gland of the oral cavity, the oesophageal glands probably secrete, continuously maintaining a thin lubricating layer of mucus on the surface of the epithelium, but the rate of their secretion may be increased during the ingestion and swallowing of food (10).

(3) Histopathology of oesophageal tumors:

(A) Squamous epithelial tumors:

1- Squamous cell papilloma:-

Squamous cell papilloma is rare and usually causes no specific symptoms. It is a benign tumor composed of hyperplastic squamous epithelium covering finger-like processes with cores derived from the lamina propria. The polypoid lesions are smooth, sharply demarcated and usually 5 mm or less in maximum diameter. Rarely, giant papillomas have been reported, with sizes up to 5 cm. Most squamous cell papillomas represent single isolated lesions, typically located in the distal to middle third of the oesophagus, but multiple lesions occur.

Histologically cores of firbovascular tissue are covered by mature stratified squamous epithelium. The aetiological role of human papillomavirus (HPV) infection has been investigated in several studies, but the results were inconclusive. Malignant progression to SCC is extremely rare.

2- Squamous cell carcinoma of the oesophagus

- Definition:-

Squamous cell carcinoma (SCC) of the esophagus is a malignant epithelial tumor with squamous cell differentiation. Microscopically it is characterized by keratinocyte-like-cells with intercellular

bridges and/or keratinization. Blacks have a fourfold to fivefold higher rate of squamous cell carcinoma than whites, but the rate of adenocarcinoma in blacks was 30% of the rate in whites. The incidence of squamous cell carcinoma in black men and women increased by approximately 30% between 1973 and 1982, and the rate of adenocarcinoma among white men increased 74%. (11)

- Epidemiology :-

Squamous cell carcinoma of the oesophagus shows great geographical diversity in incidence, mortality and sex ratio. There are however, several well-defined high-risk areas e.g. Normandy and Calvados in North-West France and Northern Italy. This type of cancer is much more frequent in Eastern countries and in many developing countries. In both high-risk and low-risk regions, this cancer is exceedingly rare before the age of 30 and the median age is around 65 in both males and females. There was no significant difference between its involvement among males and females (12). In the past 20-30 years the incidence of squamous cell carcinoma (SC) of the esophagus in western countries has largely stayed constant, while that of adenocarcinoma (AC) of the oesophagus and the cardia has risen. (13).

- Etiology:-

1- Tobacco and alcohol:- In Western countries, nearly 90% of the risk of SCC can be attributed to tobacco and alcohol. With regard to the consumption of tobacco, a moderate intake during a long period carries a higher risk than a high intake during a shorter period, whereas the reverse is true for alcohol. The oesophagus, stomach and pancreas are primary target organs for ethanol-related diseases. In the oesophagus and stomach, ethanol induces motility disorders and mucosal lesions that are dose-dependent

and reversible under acute conditions. Chronic consumption of alcohol causes a significant increase in the risk for squamous carcinoma of the oesophagus. All of these effects are mainly caused by direct contact of alcohol or its metabolite acetaldehyde with the mucosa. Non-alcoholic components are responsible for many effects of alcoholic beverages, including the powerful stimulation of gastric acid secretion by beverages that are produced by fermentation. (14), Alterations of retinoic acid receptors protein may contribute in the development of SCC in esophagus and that in some patients life style (e.g. smoking and alcohol consumption) may be a critical component in the alteration of retinoic acid receptor levels in esophagus (15). Because some of the causes of increased mean corpuscular volume (MCV) and oesophageal squamous cell carcinoma (OSCC) , including alcoholism, acetaldehyde exposure, smoking, and poor nutrition are common to both, macrocytosis has been used as a predictor of early OSCC in alcoholics. MCV and alcohol flushing might be used to better select candidates to screen this high-mortality-rate cancer not only in alcoholics but also in nonalcoholic men (16).

2- Nutrition:-In high-risk areas of China, a deficiency in certain trace elements and the consumption of pickled or mouldy foods (which are potential sources of nitrosamines) have been suggested . Dietary folate has been inversely related to the risk of several cancers. Although, studies on the role of dietary folate in oesophageal cancer are scanty, dietary folate was inversely related to OSCC risk (17).

3- Hot beverages:- Worldwide, one of the most common risk factors appears to be the consumption of burning-hot beverages which cause thermal injury leading to chronic oesophagitis and

then to precancerous lesions. A controversial nationwide population-based case-control study in Sweden about the relation between hot beverage consumption and oesophageal cancer concluded that, drinking beverages very hot did not increase the risk for oesophageal squamous cell carcinoma, oesophageal adenocarcinoma, or gastric cardia adenocarcinoma .(18).

4- HPV:- Conflicting reports have proposed a role for infectious agents, including human papillomavirus (HPV) infection. Associations between achalasia, Plummer-Vinson syndrome, celiac disease and tylosis (focal noneepidermolytic palmoplantar keratoderma) with oesophageal cancer have also been described.

- Localization:-

Oesophageal SCC is located predominantly in the middle and the lower third of the oesophagus, only 10-15% being situated in the upper third. Nearly half of the SCC occurred in the middle of the oesophagus (11)

- Macroscopy:-

The gross appearance varies according to whether it is detected in an early or an advanced stage of the disease. Among early SCC, polypoid, plaque-like, depressed and occult lesions have been described. For the macroscopic classification of advanced oesophageal SCC, Ming has proposed three major patterns: fungating, ulcerative and infiltrating. The fungating pattern is characterized by a predominantly exophytic growth, whereas in the ulcerative pattern, the tumor growth is predominantly intramural, with a central ulceration and elevated ulcer edges. The infiltrative pattern, which is the least common one, also shows a predominantly intramural growth, but causes only a small mucosal defect (2).

- **Precursor lesions:-**

The development of oesophageal SCC is thought to be a multistage process which progresses from the conversion of normal squamous epithelium to that with basal cell hyperplasia, intraepithelial neoplasia (dysplasia and carcinoma in situ), and finally, invasive SCC (2).

Basal cell hyperplasia:-

This lesion is histologically defined as an otherwise normal squamous epithelium with a basal zone thickness greater than 15% of total epithelial thickness, without elongation of lamina propria papillae. In most cases, basal cell hyperplasia is an epithelial proliferative lesion in response to oesophagitis, which is frequently observed in high-risk populations for oesophageal cancer (2).

Intraepithelial neoplasia:-

The lesion is about eight times more common in high cancer-risk areas than in low-risk areas and is frequently found adjacent to invasive SCC in oesophagectomy specimens. Morphological features of intraepithelial neoplasia include both architectural and cytological abnormalities. The architectural abnormality is characterized by a disorganization of the epithelium and loss of normal cell polarity. Cytologically, the cells exhibit irregular and hyperchromatic nuclei, an increase in nuclear/cytoplasmic ratio and increased mitotic activity. Dysplasia is usually graded as low or high-grade. In low-grade dysplasia, the abnormalities are often confined to the lower half of the epithelium, whereas in high-grade dysplasia the abnormal cells also occur in the upper half and exhibit a greater degree of atypia. In carcinoma in situ, the atypical cells are present throughout the epithelium without

evidence of maturation at the surface of the epithelium. In a two-tier system, severe dysplasia and carcinoma-in-situ are included under the rubric of high-grade intraepithelial neoplasia, and may have the same clinical implications (2).

Epidemiological follow-up studies suggest an increased risk for the subsequent development of invasive SCC for patients with basal cell hyperplasia (relative risk: 2.1), low-grade dysplasia (RR: 2.2), moderate-grade dysplasia (RR: 15.8), high-grade dysplasia (RR: 72.6) and carcinoma in situ (RR: 62.5).(2)

-Tumor spread and staging:-

Tumor spread:-

The most common sites of metastasis of oesophageal SCC are the regional lymph nodes. The risk of lymph node metastasis is about 5% in carcinomas confined to the mucosa but over 30% in carcinomas invading the sub mucosa and over 80% in carcinomas invading adjacent organs or tissues. Lesions of the upper third of the oesophagus most frequently involve cervical and mediastinal lymph nodes, whereas those of the middle third metastasise to the mediastinal, cervical and upper gastric lymph nodes. Carcinomas of the lower third preferentially spread to the lower mediastinal and the abdominal lymph nodes. The most common sites of haematogenous metastases are the lung and the liver. Less frequently affected sites are the bones, adrenal glands and brain. (2)

Superficial oesophageal carcinoma:-

When the tumor is confined to the mucosa or the sub mucosa, the term superficial oesophageal carcinoma is used

irrespective of the presence of regional lymph node metastases (2). **Intramural metastases:-**

A special feature of oesophageal SCC is the occurrence of intramural metastases. These metastases are thought to result from intramural lymphatic spread with the establishment of secondary intramural tumor deposits. Intramural metastases are associated with an advanced stage of disease and with shorter survival (2).

Second primary SCC:-

Additionally, the occurrence of multiple independent SCC has been described in between 14and 31% of cases, the second cancers being mainly carcinomas in situ and superficial SCC.

Staging:

For the staging of SCC, the TNM system (tumor, node, metastasis) established by the international Union Against Cancer (UICC) is the most widely used system. Its usefulness in the planning of treatment and in the prediction of prognosis has been validated (Appendix 2).

Histopathology:-

Oesophageal SCC is defined as the penetration of neoplastic squamous epithelium through the epithelial basement membrane and extension into the lamina apropria or deeper tissue layers. Invasion commonly starts from a carcinoma in situ with the proliferation of rete-like projections of neoplastic epithelium that push into the lamina propria with subsequent dissociation into small carcinomatous cell clusters. Along with vertical tumor cell infiltration, usually a horizontal growth undermines the adjacent normal mucosa at the tumor periphery. The carcinoma may already invade intramural lymphatic vessels and veins at an early

stage of disease. The frequency of lymphatic and blood vessel invasion increases with increasing depth of invasion. Tumor cell in lymphatic vessels and in blood vessels may be found progressively several centimeters beyond the gross tumor. The carcinoma invades the muscular layers, enters the loose fibrous adventitia and may extend beyond the adventitia, with invasion of adjacent organs or tissues, especially the trachea and bronchi, eventually with the formation of oesophagotracheal or oesophagobronchial fistulae (2).

Oesophageal SCC displays different microscopic patterns of invasion, which are categorized as 'expansive growth' or 'infiltrative growth'. The former pattern is characterized by a broad and smooth invasion front with little or no tumor cell dissociation, whereas the infiltrative pattern shows an irregular invasion front and a marked tumor cell dissociation.

The degree of desmoplastic or inflammatory stromal reaction, nuclear polymorphism and keratinization is extremely variable. Additionally, otherwise typical oesophageal SCC may contain small foci of glandular differentiation, indicated by the formation of tubular glands or mucin-producing tumor cells.

Variants of squamous cell carcinoma :

- Verrucous carcinoma:-

This rare variant of squamous cell carcinoma is histologically comparable to verrucous carcinomas arising at other sites. On gross examination, its appearance is exophytic, warty, cauliflower-like or papillary. It can be found in any part of the oesophagus. Histologically, it is defined as a malignant papillary tumor composed of well differentiated and keratinized squamous epithelium with minimal cytological atypia, and pushing rather than

infiltrating margins. Oesophageal verrucous carcinoma grows slowly and invades locally, with a very low metastasizing potential (2).

- Spindle cell carcinoma

This unusual malignancy is defined as a squamous cell carcinoma with a variable sarcomatoid spindle cell component. It is also known by a variety of other terms, including carcinosarcoma, pseudosarcomatous squamous cell carcinoma, polypoid carcinoma and squamous cell carcinoma with a spindle cell component. Macroscopically, the tumor is characterized by a polypoid growth pattern. The spindle cells may be capable of maturation, forming bone, cartilage and skeletal muscle cells. Alternatively, they may be more pleomorphic, resembling malignant fibrous histocytoma. In the majority of cases a gradual transition between carcinomatous and sarcomatous components has been observed on the light microscopic level. Immunohistochemical and electron microscopic studies indicate that the sarcomatous spindle cells show various degrees of epithelial differentiation. Therefore, the sarcomatous component may be metaplastic. However, a recent molecular analysis of a single case of a spindle cell carcinoma showed divergent genetic alterations in the carcinomatous and in the sarcomatous tumor component suggesting two independent malignant cell clones (2).

Basaloid squamous cell carcinoma:-

This rare but distinct variant of oesophageal SCC appears to be identical to the basaloid squamous cell carcinomas of the upper aerodigestive tract. Histologically, it is composed of closely packed cells with hyperchromatic nuclei and scant basophilic cytoplasm, which show a solid growth pattern, small gland-like

spaces and foci of comedo-type necrosis. Basaloid squamous cell carcinomas are associated with intraepithelial neoplasia, invasive SCC or islands of squamous differentiation among the basaloid cells. The proliferative activity is higher than in typical SCC. However, basaloid squamous cell carcinoma is also characterized by a high rate of apoptosis and its prognosis does not differ significantly from that of the ordinary oesophageal SCC (2).

Grading:-

Grading of oesophageal SCC is traditionally based on the parameters of mitotic activity, anisonucleosis and degree of differentiation (2).

Well differentiated tumors have cytological and histological features similar to those of the normal oesophageal squamous epithelium. In well differentiated oesophageal SCC there is a high proportion of large differentiated, keratinocyte-like squamous cells and a low proportion of small basal-type cells, which are located in the periphery of the cancer cell nests. The occurrence of keratinization has been interpreted as a sign of differentiation, although the normal oesophageal squamous epithelium does not keratinize (2).

Poorly differentiated tumors predominantly consist of basal-type cells, which usually exhibit a high mitotic rate.

Moderately differentiated carcinomas, between the well and poorly differentiated types, are the most common type, accounting for about two-thirds of all oesophageal SCC.

Undifferentiated carcinomas are defined by a lack of definite light microscopic features of differentiation. However, ultrastructural or immunohistochemical investigations may disclose

features of squamous differentiation in a subset of light-microscopically undifferentiated carcinomas (2).

Clinical features:-

Symptoms and signs:-

The most common symptoms of advanced oesophageal cancer are dysphagia, weight loss, retrosternal or epigastric pain and regurgitation caused by narrowing of the oesophageal lumen by tumor growth. Superficial SCC usually has no specific symptoms but sometimes causes a tingling sensation.

Endoscopy and vital staining:-

Chromoendoscopy utilizing toluidine blue or Lugol iodine spray may be of value. Toluidine blue, a metachromatic stain from the thiazine group, has a particular affinity for RNA and DNA and stains areas that are richer in nuclei than the normal mucosa. Lugol solution reacts specifically with glycogen in the normal squamous epithelium, whereas precancerous and cancerous lesions, but also inflamed areas and gastric heterotopia, are not stained. However, the superficial extension of carcinomas confined to the mucosa can not be clearly recognized by simple endoscopy.

Endoscopic ultrasonography:-

Endoscopic ultrasonography is used to evaluate both depth of tumor infiltration and para-oesophageal lymph node involvement in early and advanced stages of the disease.

-**Computed tomography** (CT) and magnetic resonance imaging (MRI):-

In advanced carcinomas, CT and MRI give information on local and systemic spread of SCC (2).

Treatment groups:-

Following the clinical staging, patients are usually divided into two treatment groups: those with locoregional disease in whom the tumor is potentially curable (e.g. by surgery, radiotherapy, multimodal therapy), and those with advanced disease (metastases outside the regional area or invasion of the airway) in whom only palliative treatment is indicated. Oesophageal SCC limited to the mucosa may be treated by endoscopic mucosal resection due to its low risk of nodal metastasis. Endoscopic mucosal resection is also indicated for high-grade intraepithelial neoplasia. Tumors that have invaded the sub mucosa or those in more advanced tumor stage have more than 30% risk of lymph node metastasis, and endoscopic therapy is not indicated. Additionally, clinical staging is performed in order to determine the success of treatment, e.g. following radio- and/or chemotherapy (2).

(B) Adenocarcinoma of the oesophagus:-

(1) Definition and epidemiology:-

It is malignant epithelial tumor of the oesophagus with glandular differentiation arising predominantly from Barrett mucosa in the lower third of the oesophagus. Infrequently, adenocrcinoma originates from heterotopic gastric mucosa in the upper oesophagus, or from mucosal and submucosal glands. In the mid 1990s the incidence of oesophageal adenocarcinoma has been estimated to be between 1 and 4 per 100.000 per year in the USA and several European countries and the incidence of oesophageal adenocarcinoma has risen considerably, now it is equally or even

more prevalent than squamous cell cancers in these regions (19), In Asia and Africa, adenocarcinoma of the oesophagus is an uncommon finding, but increasing rates are also reported from these areas, these include a high preponderance for the male sex (male: female ratio 7:1) . (20), (21), a higher incidence among whites and an average age at the time of diagnosis of around 65 years. The striking male predominance in patients with adenocarcinoma of the oesophagus (male to female ratio of 6:1) is not explained by known risk factor (22).

(2) Aetiology:-

1- Barrett oesophagus: Barrett's esophagus is a premalignant condition and remains the number one risk factor for developing adenocarcinoma. Gastro-esophageal reflux disease is a strong risk factor for both esophageal adenocarcinoma and the precancerous lesion Barrett's esophagus. Both of these conditions are related to the reflux of acid and bile into the esophagus. This results in inflammation and cell damage which initiates a sequence of events termed the metaplasia-dysplasia sequence in which the squamous epithelium is replaced by columnar epithelium exhibiting increasing degrees of dysplasia and overt malignancy. Barrett's esophagus is being better recognized in patients presenting with extra-esophageal symptoms of gastroesophageal reflux such as chronic cough and asthma (23). Barrett's esophagus is generally accepted as a complication of chronic and severe gastroesophageal reflux disease (GERD) (24). Experimental and clinical data indicate that combined oesophageal exposure to gastric acid and duodenal contents (bile acids and pancreatic enzymes) appears to be more detrimental than isolated exposure to gastric juice or duodenal

contents alone. Recent reports from some surgical series further suggest the importance of gastric and even duodenal reflux in the etiology of esophageal metaplastic development (23). Combined reflux is thought to increase cancer risk by promoting cellular proliferation and by exposing the oesophageal epithelium to potentially genotoxic gastro and intestinal contents e.g. nitrosamines. However, the risk for patients with Barrett esophagus to develop esophageal adenocarcinoma is low, and most patients undergoing surveillance will not develop malignancy (25). **Clinically** Barrett's esophagus is silent in up to 90% of cases. **Histopathologically,** Barrett epithelium is characterized by two different types of cells, i.e. goblet cells and columnar cells and has also been termed ‘specialized’, ‘distinctive’ or Barrett metaplasia. The goblet cells stain positively with Alcian blue at low pH (2.5). The metaplastic epithelium has a flat or villiform surface, and is identical to gastric intestinal metaplasia of the incomplete type (type II or III). Rarely, foci of complete intestinal metaplasia (type I) with absorptive cells and Paneth cells may be found. The mucous glands beneath the surface epithelium and pits may also contain metaplastic epithelium. Recent studies suggest that the columnar metaplasia originates from multipotential cells located in intrinsic oesophageal glands.

Intraepithelial neoplasia in Barrett oesophagus

Generally has no distinctive gross features and is detected by systematic sampling of a flat Barrett mucosa. The area involved is variable, and the presence of multiple dysplastic foci is common.In some cases, intraepithelial neoplasia presents as one of several nodular masses resembling sessile adenomas. Here dysplastic lesions have been considered true adenomas, with an expanding

but localized growth resulting in a well demarcated interface with the surrounding tissue. Epithelial atypia in Barrett mucosa is usually assessed according to the system devised for atypia in ulcerative colitis, namely: negative, positive or indefinite for intraepithelial neoplasia. If intraepithelial neoplasia is present, it should be classified as low-grade (synonymous with mild or moderate dysplasia) or high-grade (synonymous with severe dysplasia and carcinoma in situ). The criteria used to grade intraepithelial neoplasia comprise cytological and architectural feature.

Negative for intraepithelial neoplasia :-

Usually the lamina propria of Barrett mucosa contains a mild accompanying inflammatory infiltrate of mononuclear cells. There may be mild reactive changes with enlarged, hyperchromatic nuclei, prominence of nucleoli, and occasional mild stratification in the lower portion of the glands. However, towards the surface there is maturation of the epithelium with few or no abnormalities.

Atypia indefinite for intraepithelial neoplasia

Is one of the major challenges for the pathologist in Barrett oesophagus in the differentiation of intraepithelial neoplasia from reactive or regenerative epithelial changes. This is particularly difficult, sometimes even impossible, if erosions or ulcerations are present . In areas adjacent to erosions and ulcerations, the metaplastic epithelium may display villiform hyperplasia of the surface foveolae with cytological atypia and architectural disturbances. These abnormalities are usually milder than those observed in intraepithelial neoplasia. There is a normal expansion of the basal replication zone in regenerative epithelium versus intraepithelial neoplasia, where the proliferation shifts to more

superficial portions of the gland. If there is doubt as to whether reactive and regenerative changes or intraepithelial neoplasia is present in a biopsy, the category atypia indefinite for intraepithelial neoplasia is appropriate and a repeat biopsy after reflux control by medical acid suppression or anti-reflux therapy is indicated.

Low-grade and high-grade intraepithelial neoplasia in Barrett metaplastic mucosa is defined as a neoplastic process limited to the epithelium. Its prevalence in Barrett mucosa is approximately 10% and it develops only in the intestinal type metaplastic epithelium. Cytological abnormalities typically extend to the surface of the mucosa. In low-grade intraepithelial neoplasia, there is decreased mucus secretion, nuclear pseudostratification confined to the lower half of the glandular epithelium, occasional mitosis, mild pleomorphism, and minimal architectural changes. High-grade intraepithelial neoplasia shows marked pleomorphism and decrease of mucus secretion, frequent mitosis, nuclear stratification extending to the upper part of the cells and glands, and marked architectural aberrations. The most severe architectural changes consist of a cribriform pattern that is a feature of high-grade intraepithelial neoplasia as long as the basement membrane of the neoplastic glands has not been disrupted. The diagnostic reproducibility of intraepithelial neoplasia is far from perfect: significant interobserver variation exists (2).

2- Tobacco:-

Smoking has been identified as another major risk factor for oesophageal adenocarcinoma and may account for as much as 40% of cases through an early stage carcinogenic effect. Placing tobacco under the tongue or in the labiodental groove seems to be

associated with a high incidence of oral cancer and possibly also of oesophageal cancer (5)

3- Obesity and diabetes mellitus:-

Obesity is a risk factor for adenocarcinomas of the oesophagus and gastric cardia. Diabetes mellitus might mediate that association, A study done by Rubenstein showed no association between diabetes mellitus and adenocarcinoma of oesophagus (26), (27).

4- Alcohol:-

In contrast to squamous cell oesophageal carcinoma, there is no strong relation between alcohol consumption and adenocarcinoma of the oesophagus. (27).

5- Helicobacter pylori:-

This infection does not appear to be a predisposing factor for the development of intestinal metaplasia and adenocarcinoma in the distal oesophagus. The relationship between H. pylori and GERD+ Barrett's esophagus is controversial. H. pylori eradication therapy may increase the risk for the development of gastroesophageal reflux disease GERD, which may lead to increase a risk factor of Barrett's esophagus and esophageal adenocarcinoma. Accordingly, gastric H. pylori infection may even exert a protective effect (24).

- Localization:-

Adenocarcinoma may occur anywhere in a segment lined with columnar metaplastic mucosa (Barrett oesophagus) but develops mostly in its proximal verge. Adenocarcinoma in a short segment of Barrett oesophagus is easily mistaken for adenocarcinoma of the cardia. Since adenocarcinoma originating from the distal oesophagus may infiltrate the gastric cardia and

carcinoma of the gastric cardia or subcardial region may grow into the distal oesophagus these entities are frequently difficult to discriminate. As an exception, adenocarcinoma occurs also in the middle or proximal third of the oesphagus, in the latter usually from a congenital islet of heterotopic columnar mucosa (that is present in up to 10% of the population) (2).

(3) Symptoms and signs Adenocarcinoma:-

Dysphagia is often the first symptom of advanced adenocarcinoma in the oesophagus. This may be associated with retrosternal or epigastric pain or cachexia. **Endoscopically,** the early stages may be that of a small polypoid adenomatous-like lesion, but more often it is flat, depressed, elevated or occult. Areas with high-grade intraepithelial neoplasia are often multicentric and occult. Therefore a systematic tissue sampling has been recommended when no abnormality is evident macroscopically. The usual pattern of advanced adenocarcinoma at endoscopy is that of an axial, and often tight, stenosis in the distal third of the oesophagus: with a polypoid tumor, bleeding occurs at contact. **Macroscopically,** the majority of primary adenocarcinomas of the oesophagus arise in the lower third of the oesophagus within a segment of Barrett mucosa. Adjacent to the tumor, the typical salmon-pink mucosa of Barrett oesophagus may be evident, especially in early carcinomas. In the early stages, the gross findings of Barrett adenocarcinoma may be subtle with irregular mucosal bumps or small plaques. At the time of diagnosis, most tumors are advanced with deep infiltration of the oesophageal wall. The advanced carcinomas are predominantly flat and ulcerated with only one third having a polypoid or fungating

appearance. Occasionally, multifocal tumors may be present. The rare adenocarcinomas arising independently of Barrett oesophagus from ectopic gastric glands and oesophageal glands display predominantly ulceration and polypoid gross features, respectively. These tumors are also found in the upper and middle third of the oesophagus, but are rare (2).

(4) Histopathology of adenocarcinoma:-

Adenocarcinomas arising in the setting of Barrett oesophagus are typically papillary and/or tubular. A few tumors are of the diffuse type and show rare glandular formations, and sometimes signet ring cells. Differentiation may produce endocrine cells, Paneth cells and squamous epithelium. Mucinous adenocarcinomas i.e. tumors with more than 50% of the lesion consisting of mucin, also occur. About **Grading;** most adenocarcinomas arising from Barrett mucosa are well or moderately differentiated, and display well formed tubular or papillary structures. The well differentiated tumors may pose a diagnostic problem in biopsy specimens because the infiltrating component may be difficult to recognize as invasive since Barrett mucosa often has irregular dispersed glands. Glandular structures are only slightly formed in poorly differentiated adenocarcinomas and absent in undifferentiated tumors. Adenocarcinomas **spread** first locally and infiltrate the oesophageal wall. Distal spread to the stomach may occur. Extension through the oesophageal wall into adventitial tissue, and then into adjacent organs or tissues is similar to squamous cell carcinoma. Common sites or local spread comprise the mediastinum, tracheobronchial tree, lung, aorta, pericardium, heart and spine. Barrett associated adenocarcinoma

metastasizes to para-oesophageal and paracardial lymph nodes, those of the lesser curvature of the stomach and the celiac nodes. Distant metastases occur late. For **staging,** the TNM classification used for SCC is applicable to Barrett adenocarcinoma and provides prognostically significant data (2).

(5) Other carcinomas:-

- Adenosquamous carcinoma:-

This carcinoma has a significant squamous carcinomatous component that is intermingled with a tubular adenocarcinoma.

- Mucoepidermoid carcinoma:-

This rare carcinoma shows an intimate mixture of squamous cells, mucus secreting cells and cells of an intermediate type.

- Adenoid cystic carcinoma:-

This neoplasm is also infrequent and believed to arise, like the mucoepidermoid variant, from oesophageal glands. Both lesions tend to be of salivary gland type, and small tumors may be confined to the submucosa.

(6) Prognostic factors in adenocarcinoma :-

The major prognostic factors in adenocarcinoma of the oesophagus are the depth of mural invasion and the presence or absence of lymph node or distant metastasis. Gross features and histological differentiation do not influence prognosis. The overall 5-year survival rate after surgery is less than 20% in most series including a majority of advanced carcinomas. The survival rates are better in superficial adenocarcinoma ranging from 65% to 80% in different series.

Since the stage at the time of diagnosis is the most important factor affecting outcome, endoscopic surveillance of Barrett patients with early detection of their adenocarcinomas, results in better prognosis in most cases (2).

(C) Endocrine tumors of the oesophagus:-

Endocrine tumors of the oesophagus are rare and include carcinoid (well differentiated endocrine neoplasm), small cell carcinoma (poorly differentiated endocrine carcinoma) and mixed endocrine-exocrine carcinoma. **Aetiologically,** patients with small cell carcinomas often have a history of heavy smoking and one reported case was associated with long standing achalasia. A case of combined adenocarcinoma and carcinoid occurred in a patient with a Barrett oesophagus. Small cell carcinoma has also been associated with Barrett oesophagus. Carcinoid tumors are typically **located** in the lower third of the oesophagus. Almost all small cell carcinomas occur in the distal half of the oesophagus.

Clinically, dysphagia, severe weight loss and sometimes chest pain are the main symptoms of endocrine tumors of the oesophagus. Patients with small cell carcinomas often present at an advanced stage. Inappropriate antidiuretic hormone syndrome and hypercalcaemia have been reported. In addition, a case of watery diarrhea, hypokalaemia, achlorohydria (WDHA) syndrome due to ectopic production of VIP by a mixed-cell (squamous-small cell) carcinoma of the oesophagus has been described.

Macroscopically, all reported oesophageal carcinoids were of large size (from 4 to 7 cm in diameter) and infiltrated deeply the oesophageal wall. Small cell carcinomas usually appear as

fungating or ulcerated masses of large size, measuring from 4 to14 cm in greatest diameter (2).

Histopathologically, all **carcinoids** so far reported in the literature have been described as deeply infiltrative tumors, with high mitotic rate and metastases. Microscopically they are composed of solid nests of tumor cells that show positive stain for Grimelius and neuron-specific enolase, and characteristic membrane-bound neurosecretory granules at ultrastructural examination. **Small cell carcinoma** of the oesophagus is indistinguishable from its counterpart in the lung according to histological and immunohistochemical features as well as clinical behaviour. The cells may be small with dark nuclei of round or oval shape and scanty cytoplasm, or be larger with more cytoplasm (intermediate cells) forming solid sheets and nests. There may be foci of squamous carcinoma, adenocarcinoma, and/or mucoepidermoid carcinoma, a finding that raises the possibility of an origin of tumor cells from pluripotent cells present in the squamous epithelium or ducts of the submucosal glands. Argyrophylic granules can be demonstrated by Grimelius stain and small dense-core granules are always detected by electron microscopy. **Mixed endocrine-exocrine carcinoma,** a rare tumor with few reported cases. There is combination of gastrointestinal type adenocarcinoma with the trabecular-acinar component of a carcinoid (2).

Prognostic factors:-Two of three oesophageal **carcinoids** from the analysis of 8305 cases of carcinoid tumors were associated with distant metastases and one of the three reported cases died 29 months after surgery. The prognosis of **small cell** carcinoma of

the oesophagus is poor, even when the primary growth is limited. The survival period is usually less than 6 months. Multidrug chemotherapy may offer temporary remission (2).

(D) Lymphoma of the oesophagus:-

Definition:- Primary lymphoma of the oesophagus is defined as an extranodal lymphoma arising in the oesophagus with the bulk of the disease localized to this site. Contiguous lymph node involvement and distant spread may be seen but the primary clinical presentation is in the oesophagus with therapy directed at this site.

Clinical features:- The oesophagus is the least common site of involvement with lymphoma in the digestive tract, accounting for less than 1% of lymphoma patients. Oesophageal involvement is usually secondary either from the mediastinum, from nodal disease or from a primary gastric location. Patients are frequently male and usually over 50 years old. Tumors involving the distal portion of the oesophagus may cause dysphagia.

Histopathology:-Primary oesophageal lymphomas may be of large B-cell type or may be low-grade B-cell MALT lymphomas. MALT lymphomas show morphological and cytological features common to MALT lymphomas found elsewhere in the digestive tract. Lymphoid follicles are surrounded by a diffuse infiltrate of centrocyte-like (CCL) cells showing a variable degree of plasma cell differentiation. Infiltration of these cells into the overlying epithelium is usually seen. In common with other sites in the digestive tract, secondary involvement of the oesophagus may occur in dissemination of any type of lymphoma. Primary

oesophageal T-cell lymphoma has been described but is exceedingly rare (2).

(E) Mesenchymal tumors of the oesophagus:-

Definition:-A variety of rare benign and malignant mesenchymal tumors that arise in the oesophagus. Among these, tumors of smooth muscle or 'stromal' type are most common.

Epidemiology:-

Sarcomas of the oesophagus accounted for 0.2% of malignant oesophageal tumors in the United States from 1973 to 1987. Males were more frequently affected than females by nearly 2:1. Adults between the 6^{th} and 8^{th} decades are primarily affected. **Leiomyoma** is the most common benign mesenchymal tumor of the oesophagus. and constitute 0.4 - 1.5% of all tumours of this organ (28), Although leiomyomas are the most common benign tumors of the esophagus, esophageal leiomyomatosis is a rare pathological entity, and pedunculated presentation is even rarer(29). Esophageal leiomyoma usually originates from the muscle layer of the esophageal wall and grows spirally around the esophageal axis. (30). It occurs in males at twice the frequency as females and has a median age distribution between 30 and 35 years, are most frequent in the lower oesophagus and begin as intramural lesions. The larger tumors can extend to mediastinum and form a predominantly mediastinal mass. Leiomyomas are usually very slow growing and often asymptomatic. Symptomatic tumors are usually greater than five centimeters in diameter (31). Diffuse leiomyomatosis of the oesophagus is a rare entity among oesophageal diseases. Histopathologically it is characterized by

diffuse hypertrophy of the muscular layer extending to the whole oesophagus predominantly in the lower third, where it can result in tumour formation. Leiomyomatosis can involve the upper part of the stomach and is frequently associated with genital or tracheobronchial (bronchitracheal) muscular localizations. Also, it can be associated with Alport's syndrome in familial cases (32). Leiomyomatosis forms worm-like intramural structures that may extend into the upper portion of the stomach. **Clinically,** dysphagia is the usual complaint, but many leiomyomas and a small proportion of stromal tumors are asymptomatic and are incidentally detected by x-ray as mediastinal masses. Since most sarcomas project into the lumen, they are relatively easy to diagnose by endoscopy or imaging studies. The endoscopic pattern is that of a submucosal tumor with a swelling of a normal mucosa. Endoscopic ultrasound helps in determining the actual size of the tumor, its position in the oesophageal wall and its eventual position in the mediastinum. Esophageal leiomyomatosis should be considered in a young patient with long-standing dysphagia in whom smooth, tapered esophageal narrowing on barium study and circumferential esophageal wall thickening on CT scan are seen. (33). **Macroscopically** Leiomyomas vary in size from a few millimeters up to 10 cm in diameter (average 2-3 cm). They can form sausage-like masses with a large longitudinal dimension or dumb-bell shaped masses with circular involvement. Large leiomyomas (over 0.5 kg) have been described. Sarcomas, most of them representing malignant gastrointestinal stromal tumors (GISTs), are typically multinodular or less commonly plaque-like masses resembling sarcomas of the soft tissues. Many oesophageal sarcomas protrude into the mediastinum.

Histopathologically, Leiomyoma is composed of bland spindle cells and shows low or moderate cellularity and slight if any mitotic activity. There may be focal nuclear atypia. The cells have eosinophilic, fibrillary, often clumped cytoplasm. Eosinophilic granulocytes and spherical calcifications are sometimes present. Leiomyomas are typically globally positive for desmin and smooth, muscle actin and are negative for CD34 and CD 117(KIT). Leiomyomas should be removed when diagnosed, even if asymptomatic, because malignancy cannot otherwise be excluded and symptoms are likely to develop if treatment is delayed or omitted (34).

Leiomyosarcoma, a malignant tumor featuring differentiated smooth muscle cells is rare in the oesophagus. In a recent series, such tumors comprised 4% of all combined smooth muscle and stromal tumors. They were large tumors that presented in older adults, and all patients died of disease. Diagnosis is based on demonstration of smooth muscle differentiation by a-smooth muscle actin, desmin or both, and lack of KIT expression.

Stromal tumors (GISTs) are rare in the oesophagus, and comprise 20-30% of the combined cases of smooth muscle and stromal tumors. Like elsewhere in the digestive system, they predominantly occur in older adults between the 6^{th} and 8^{th} decades, oesophageal stromal tumors may have a male predominance. Most oesophageal examples are spindle cell tumors, and a minority is epithelioid. Oesophageal GISTs are identical with their gastric counterparts by their positivity for KIT and CD 34, variable reactivity for smooth muscle actin and general negativity for desmin. Most are clinically malignant, and commonly develop liver metastases. The oesophageal tumors analyzed to

date have shown similar c-kit mutations (exon 11) as observed in gastric and intestinal GISTs.

Prognosis:- The prognosis of oesophageal sarcomas, like carcinomas, is largely dependent on the size, depth of invasion and presence or absence of metastasis.

(F) Melanoma of the oesophagus:-

Malignant melanoma in the oesophagus is much more commonly metastatic than primary. Primary malignant melanoma of the esophagus is rare, and its symptoms are similar to those of squamous cell carcinoma (35), (36). Primary oesophageal melanomas are usually polypoid and are clinically aggressive lesions. They are believed to arise from a zone of atypical junctional proliferation of melanocytes and such a proliferation is often present adjacent to the invasive tumor, although it may not be observed in advanced disease. The histology of the invasive component is indistinguishable from cutaneous melanoma. Growth is typically expansile rather than infiltrative.. In a case report, melanoma was misdiagnosed in biopsy taken during endoscopy. Final precise establishing the character of the lesion was able during histopathological examination of the specimen obtained during surgery. The outcome of the treatment was poor--survival time did not exceed 14 months. Patient died because of pulmonary metastases. (37). The clinical presentation of this uncommon tumour is similar to esophageal carcinoma and the preoperative diagnosis may be difficult and total esophagectomy is the treatment of choice (38).

(G) Secondary tumors of the oesophagus:-

Definition:- Tumors of the oesophagus that originate from but are discontinuous with a primary tumor elsewhere in the oesophagus or an extra-oesophageal neoplasm.

Incidence:- Metastatic spread to the oesophagus is uncommon. An unusually high frequency (6.1% of autopsy cases) was reported from Japan.

Origin of metastases:- Neoplasms of neighbouring organs such as pharynx or gastric cardia can spread to the oesophagus via lymphatics. Haematogenous metastases from any primary localization may occur. Reported primary sites include thyroid, lung, breast, skin, kidney, prostate and ovary.

Localization:- The most common site of involvement is the middle third of the oesophagus.

Clinical features:- The leading symptom is dysphagia whereas achalasia and upper gastrointestinal bleeding with anaemia are unusual . Barium swallow examination, endoscopy, computed tomography and magnetic resonance imaging demonstrate in most cases a submucosal tumor, but any aspect resembling a primary oesophageal carcinoma may be observed.

Histopathological and predictive factors:- Submucosal localizaiotn without invasion of the mucosa is characteristic for a metastasis. Early metastases of gastric and oesphageal tumors into the oesophagus may be local indicators of systemic spread. The presence of metastasis in the oesphagus is a sign of poor prognosis, but the outcome is much better when the primary tumor growth rate is slow and when other metastases are excluded.

General objective:

-To study oesophageal tumours in Sudanese patients.

Specific Objective:

1- To identify the different histopathological patterns of oesophageal tumours in Sudanese patients.
2- To know the sex distribution among Sudanese patients with oesophageal tumours.
3- To determine the age distribution among Sudanese patients with oesophageal tumours.

Chapter 2

Materials and method

***** The study design :

This is a descriptive retrospective study done in Ibn Sina Hospital and the National Health Laboratory (N.H.L) in Khartoum, Sudan. Ibn Sina Hospital is a specialized hospital in renal and gastrointestinal diseases. It receives patients from different regions of Sudan for diagnosis and management. The National Health Laboratory is a national reference laboratory in Khartoum, Sudan.

* The study population :

The study include all patients with oesophageal tumours presented to Ibn Sina hospital and the National Health Laboratory between January 2000 through to December 2004.

* Inclusion criteria :

All patients with oesophageal tumours who underwent endoscopic or histopathologic studies for diagnosis.

* Exclusion criteria :

Patients who had no histopathological slides in the histopathology laboratory of Ibn Sina hospital and the National Health Laboratory.

* Tools of data collection:

Data is collected in a predesigned questionnaire with detailed history and investigation. The slides of histopathological diagnosis for all patients were collected and revised to confirm the diagnosis and to determine the histopathological type using the WHO classification of oesophageal tumours (appendix 1) and grades the tumour using the well differentiated, moderately differentiated and poorly differentiated grading system.

The data is electronically analysed using the computer program SPSS. A P-value of < 0.05 is considered significant.

Chapter 3

Results

About 102 cases of oesophageal biopsies were studied. All were malignant. The age and sex distribution, presenting symptoms, sites, histopathological pattern, and the behaviour of the tumour were recorded and the following results obtained:

(1) Age Distribution:

The ages range from 29 years to 90 with the mean age 65 years. 60% of patients are above 60 years, 39% between 30 and 60 years, and 1 % below 30 years. (Figure 1).

(2) Sex distribution:

Forty five patients (44%) were males and 56% were females with a ratio of female to male of 1.3: 1, (Figure 2). In squamous cell carcinoma 34 patients (38%) were males and 56 patients (62%) were females, with a female to male ratio of 1.6:1. In adenocarcinoma ten patients were males (91%) and only one patient was a female (9%), with a male to female ratio of 10:1. (Table 1).

(3) Clinical symptoms:

93 patients (91%) presented with dysphagia, 6 patients (6%) presented with dysphagia and weight loss and one patient (1%) presented with dysphagia and retrosternal pain. Two patients (2%) presented with weight loss only. (Table 2).

(4) Site distribution of the tumours:

For squamous cell carcinoma 34 patients (38%) had the tumour in the distal third of the oesophagus, 45 patients (50%) in the middle third and 11 patients (12%) in the upper third. (Figure 3). For adenocarcinoma:

10 patients (90%) in the lower third and one patient (10%) in the middle third. No one was found in the upper third. (Table 3).

(5) Histopathological pattern:

For squamous cell and its variants: 84 cases (82%) of all the oesophageal tumours were squamous cell carcinoma, 4 cases (4%) basaloid squamous cell carcinoma, 2 cases (2%) spindle cell carcinoma. For adenocarcinoma and its variants: 9 cases (9%) of all the oesophageal tumours were adenocarcinoma, one case (1%) papillary carcinoma, and one case (1%) signet ring cell carcinoma. (Table 4).

(6) Grading:

For squamous cell carcinoma: moderately differentiated 43 cases (48%), poorly differentiated 30 cases (33 %), and well differentiated 17 cases (19 %) . (Table 5). For adenocarcinoma moderately differentiated 7 cases (64%), poorly differentiated one case (9%), well differentiated 3 cases (27 %). (Table 6).

(7) Invasion of squamous cell carcinoma

80 cases (88%) were invasive, and 11 cases (12%) were intraepithelial neoplasia. (Figure 4).

Figure (1) Age distibutionin oesophageal tumours in years

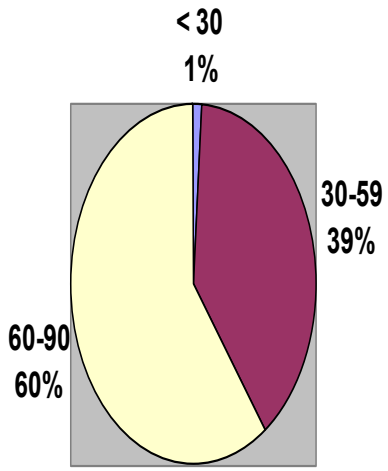


Figure (2) Sex distribution in oesophageal tumours

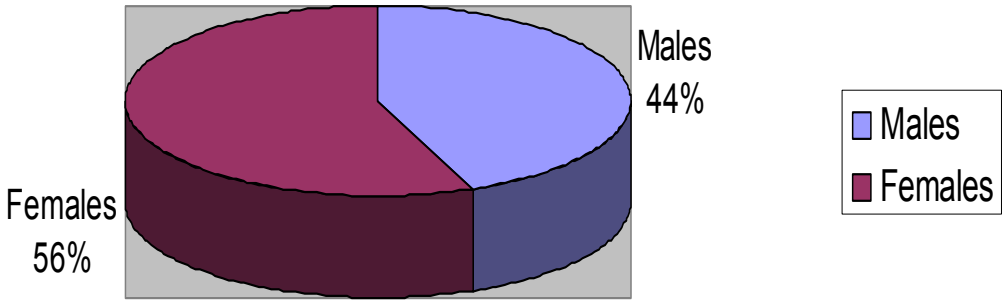


Figure (3) Site distribution of SCC.

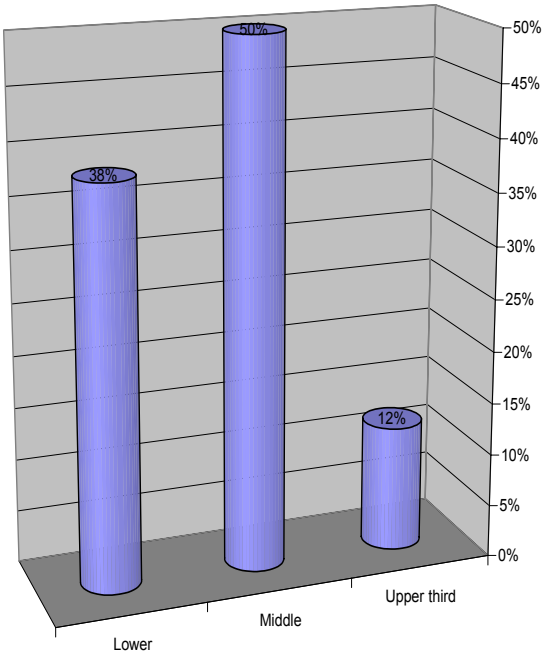
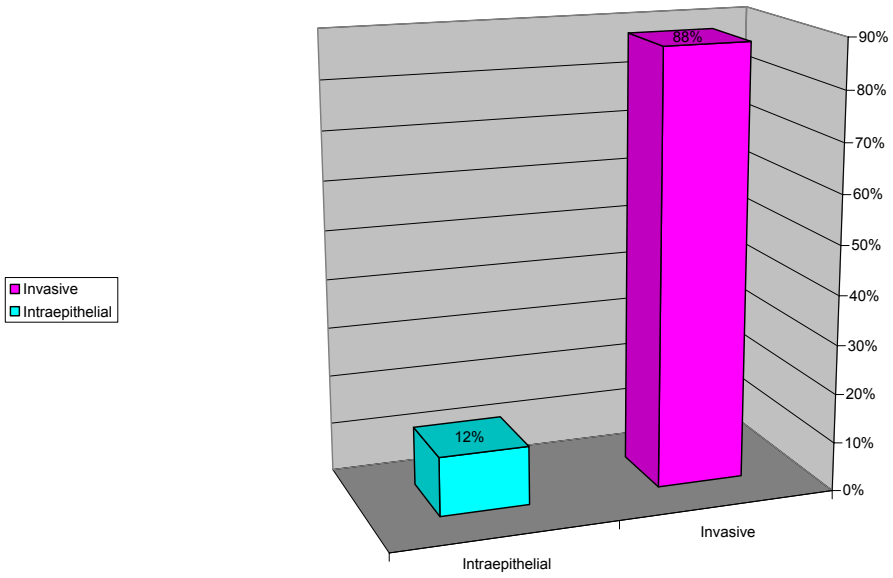


Figure (4) Invasion of SCC.



Type	Male	Female	Total	Percent
Squamous cell	34 (38%)	56 (62%)	90	88 %
Adenocarcinoma	10 (91%)	1 (9%)	11	11 %
Undifferentiated	-	1	1	1 %
Total	44 (43%)	58 (57%)	102	100 %

Table (1) Types of esophageal cancer

Symptom	Number of patients.	Percent
Dysphagia	93	91 %
Dysphagia + wt loss	6	6 %
Dysphagia + retrosternal pain	1	1 %
Wt loss only	2	2 %
Total	102	100 %

Table (2) Presenting symptoms

Site	No.	Percent
Middle third	1	10 %
Lower third	10	90 %
Total	11	100 %

Table (3) Site of the tumour

Type	No.	Percent
*Squamous cell carcinoma	84	82 %
-Basoloid Squamous cell carcinoma	4	4 %
-Spindle cell carcinomqa	2	2 %
*Adenocarcinoma	9	9 %
-Papillary Adenocarcinoma	1	1 %
-Signet ring cell carcinoma	1	1 %
* Undifferentiated	1	1%
Total	102	100 %

Table (4) Histolopathological pattern of esophageal tumors :

Differentiation	No.	Percent
Well differentiated	17	19 %
Moderately differentiated	43	48 %
Poorly differentiated	30	33 %
Total	90	100 %

Table (5) Grading of squamous cell carcinoma

Differentiation	No.	Percent
Well differentiated	3	27 %
Moderately differentiated	7	64 %
Poorly differentiated	1	9 %
Total	11	100 %

Table (6) Grading of adenocarcinoma

:

Chapter 4

Discussion

This is a descriptive retrospective study about oesophageal tumours in Sudanese patients. It includes 102 cases. All were found to be malignant tumours, the histology of which is squamous cell carcinoma and adenocarcinoma. This is consistent with the fact that benign tumours like leiomioma and other malignant tumours like endocrine tumours and lymphomas are rare as mentioned in the literature.

In Sudan as in many developing countries, there is at present no reliable statistical information on absolute cancer rate. In this study, the result is in accordance with the world wide acceptance that SCC is the most common oesophageal cancer representing 89.1%.

Sex distribution:

The male to female ratio for SCC in Sudanese patients did not change over the last 20 years. In this study it is found to be 1:1.26 compared to an older study done in 1987 which showed a ratio of 1:1.25 (39). In Pakistan the ratio is 1:1.2 almost the same. However, studies in Thailand and USA showed male predominance, 3.45:1 and 3:1 respectively. This puzzling epidemiologic contrast is not explained.

For adenocarcinoma there is striking male predominance, 10:1 which is a similar finding in many studies in different countries. It was hypothesized that sex hormones could be responsible for that sex imbalance. However, a Swedish study concluded that there is no role of sex hormones in the aetiology of oesophageal adenocarcinoma. Another study done in the USA showed that the ratio is 7:1 in whites and 10:1 in blacks (11). This may suggest a genetic implication and this merit further investigation.

Age distribution:

The ages of the patients range from 29-90 years, with a mean of 65 years. The commoner age group was 60-90 years for both SCC and adenocarcinoma, which is the same age group in Almasri SH study in the period 1965-1974 in Sudan (5). One case was found to be basaloid squamous cell carcinoma and it was found in young age group (29 years). This result goes with the international age distribution of oesophageal malignancy.

Presenting symptoms:

Dysphagia was the most frequent symptom and unfortunately a late warning one. Other symptom noticed was weight loss. These symptoms were the same worldwide and are the most bothering signs that lead the patient to seek medical advice.

Site of the tumour:

Fifty percent of SCC occurred in the middle third and 38% in the lower third in accordance with many studies done in the USA, Nigeria and other countries. The majority of adenocarcinoma arouse in the lower third because most of which arise in Barret oesophagus.

Histological pattern:

In this study, the SCC variants basaloid cell carcinoma and spindle cell carcinoma were commoner in females while adenocarcinoma with its different histological patterns, namely papillary adenocarcinoma and signet ring carcinoma were found in males. One case was undifferentiated carcinoma and was a female. The majority of squamous cell and adenocarcinomas were

moderately differentiated. However the prognostic impact of tumour differentiation is equivocal possibly due poor standardization of the grading system and to the high prognostic power of tumour stage (WHO). Invasive squamous cell carcinomas represent the majority of cases (88%) while the rest were intraepithelial neoplasia. This implies that, the diagnosis of oesophageal cancer is usually late and necessitates the need for mass screening particularly for high risk patients.

Conclusion

1- Benign Oesophageal tumours and some malignant tumours like endocrine tumours and lymphomas are rare in Sudan.
2- The most common type of oesophageal cancer in Sudan is squamous cell carcinoma
3- There is striking male predominance in Sudanese patients with adenocarcinoma.
4- The male to female ratio in Sudanese patient with squamous cell carcinoma remained static over the last twenty years.
5- The common age group for oesophageal cancer in Sudanese patients is 60-90 years.

Recommendation

It is recommended that:

(1) Establishment of screening programs for oesophageal carcinoma for the high risk group.

(2) Further studies should be carried out to clarify exact risk factors.

(3) Detailed histopathological diagnosis and staging is needed.

(4) Provision of histopathology facilities for all regional hospitals.

(5) The statistical and registry services should be improved at both national and regional levels.

Appendix

Appendix (1) WHO histological classification of esophageal tumors

Epithelial tumors	**Non-epithelial tumors**
Squamous cell papilloma	Leiomyoma
Intraepithelial neoplasia	Lipoma
Squamous	Granular cell tumor
Glandular (adenoma)	Gastrointestinal stromal tumor
Carcinoma	Benign
Squamous cell carcinoma	Uncertain malignant potential
Verrucous (squamous) carcinoma	Malignant
Basaloid squamous cell carcinoma	Leiomyosarcoma
Spindle cell (squamous) carcinoma	Rhabdomyosarcoma
Adenocarcinoma	Kaposi sarcoma
Adenosquamous carcinoma	Malignant melanoma
Mucoepidermoid carcinoma	Others
Adenoid cystic carcinoma	Secondary tumors
Small cell carcinoma	
Undifferentiated carcinoma	
Others	
Carcinoid tumor	

Appendix (2): TNM classification of oesophageal tumors

T-	Primary tumor
TX	Primary tumor cannot be assessed
TO	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or sub mucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
N-	Regional lymph nodes
N+	Regional lymph nodes cannot be assessed
NO	No regional lymph node metastasis
N1	Regional lymph node metastasis
M-	Distant metastasis
M+	Distant metastasis cannot be assessed
MO	No distant metastasis
M1	Distant metastasis

For tumors of lower thoracic oesophagus

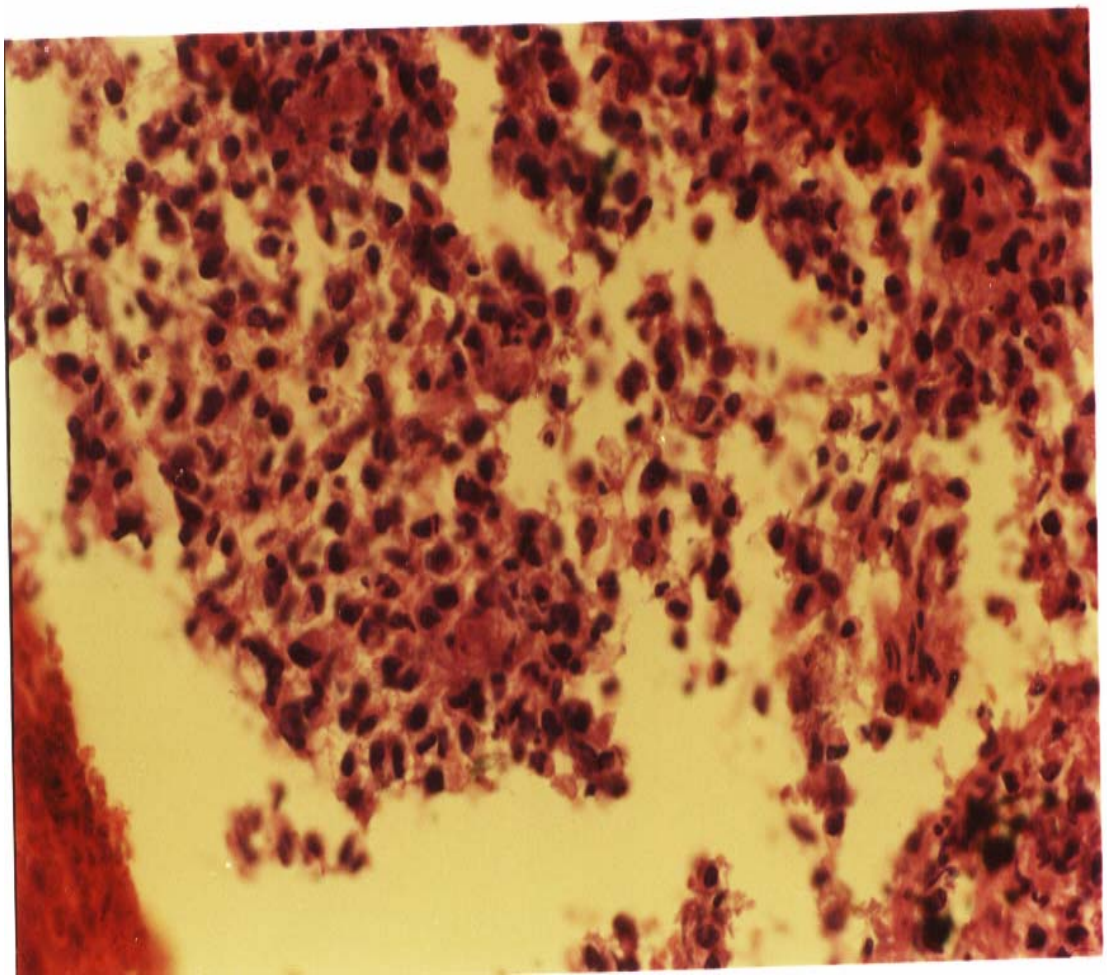
M1a	Metastasis in celiac lymph nodes
M1b	other distant metastasis

Appendix (3) Data sheet

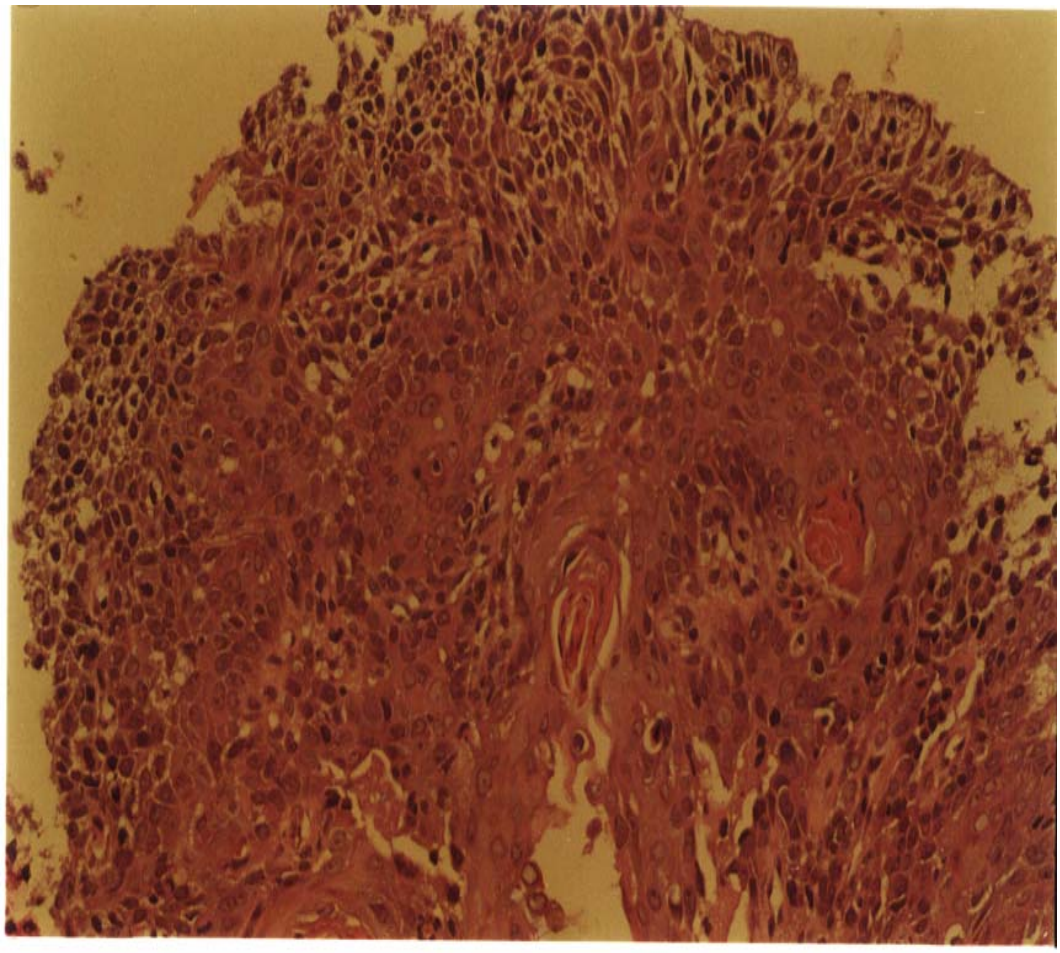
1- Name 2- Lab No
3- Residence 4- Age
5- Sex Male [ ] Female [ ]
6- Tribe
7- Clinical remarks:
a- Not written [ ]
b- Dysphagia [ ]
c- Wt loss [ ]
d- Others [ ]
8-Biopsy report:
a- Site of the tumor
b- Gross appearance
c- Others
d- No report
8-Histopathology report:
a- Squamous cell carcinoma:
1- Differentiation
Well [ ] Moderate [ ] Poor [ ]
2- Variants
- Spindle cell [ ]
- Pseudosarcoma [ ]
-Verrucous carcinoma [ ]
3- Carcinoma in situ [ ]
4- Dysplasia [ ]
b- Adenocarcinoma differentiation
Well [ ] Moderate [ ] Poor [ ]
c- Other tumours

d- Notes and comments

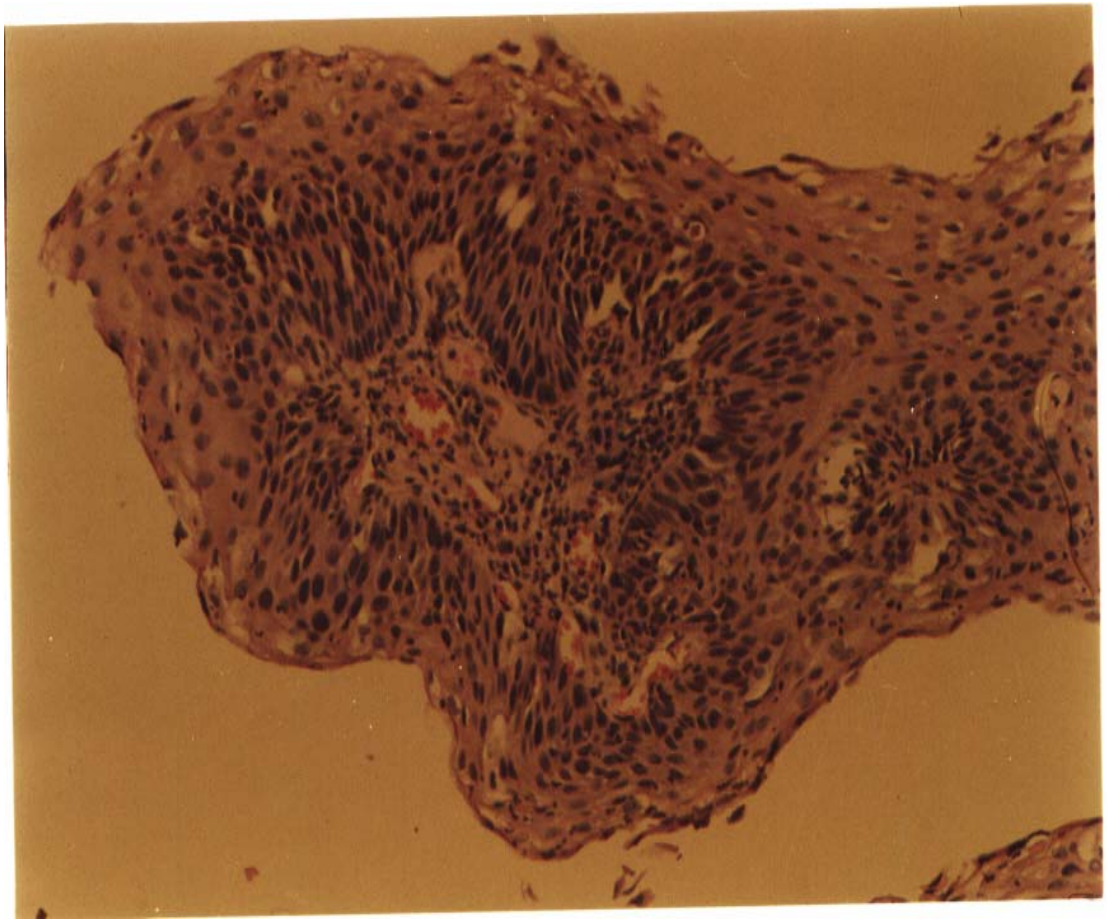
Appendix (4) Slides:



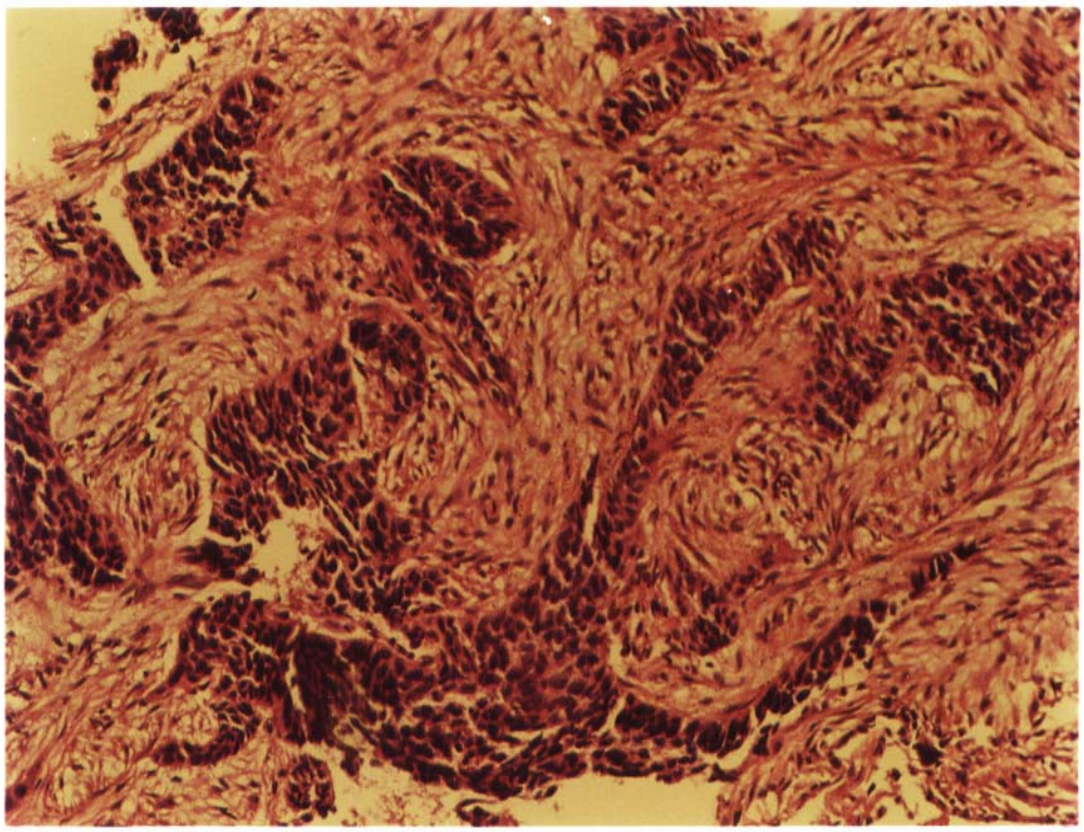
Slide (1) :Undifferentiated carcinoma. No glandular or squamous structure (H&E X40)



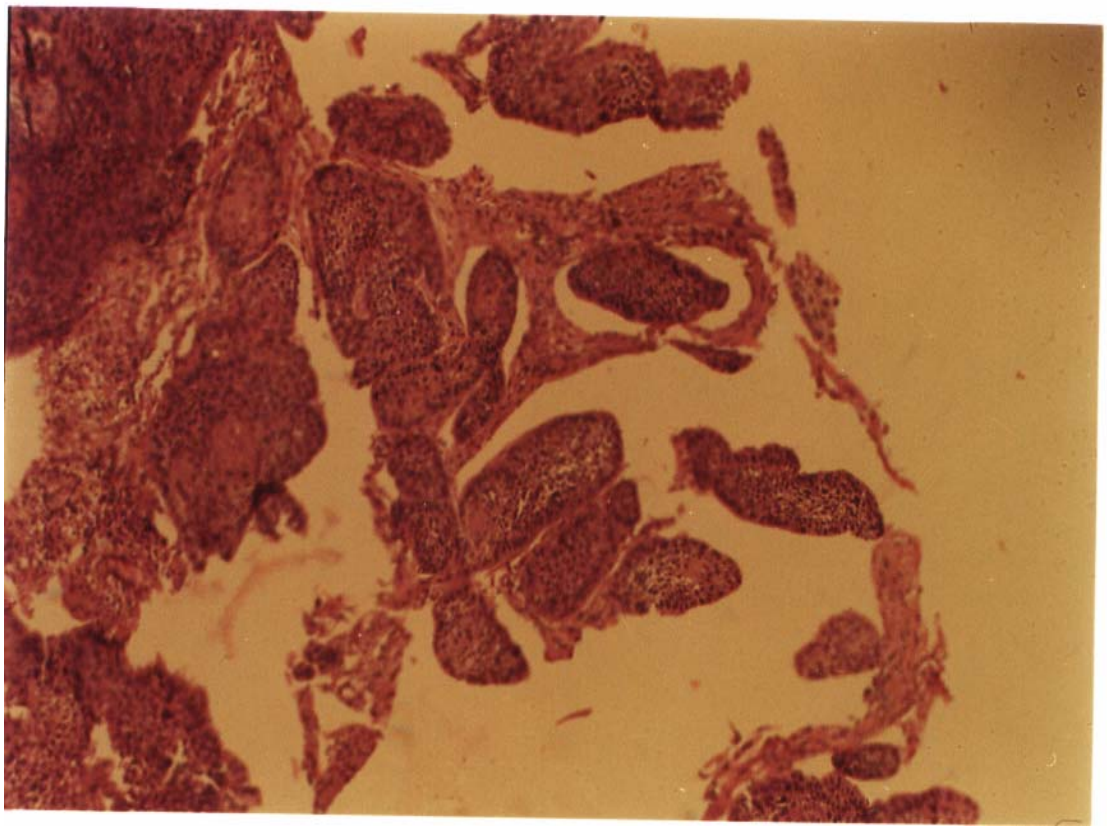
Slide (2) **Well differentiated squamous cell carcinoma, showing two squamous cell nests with keratin (H&E X20).**



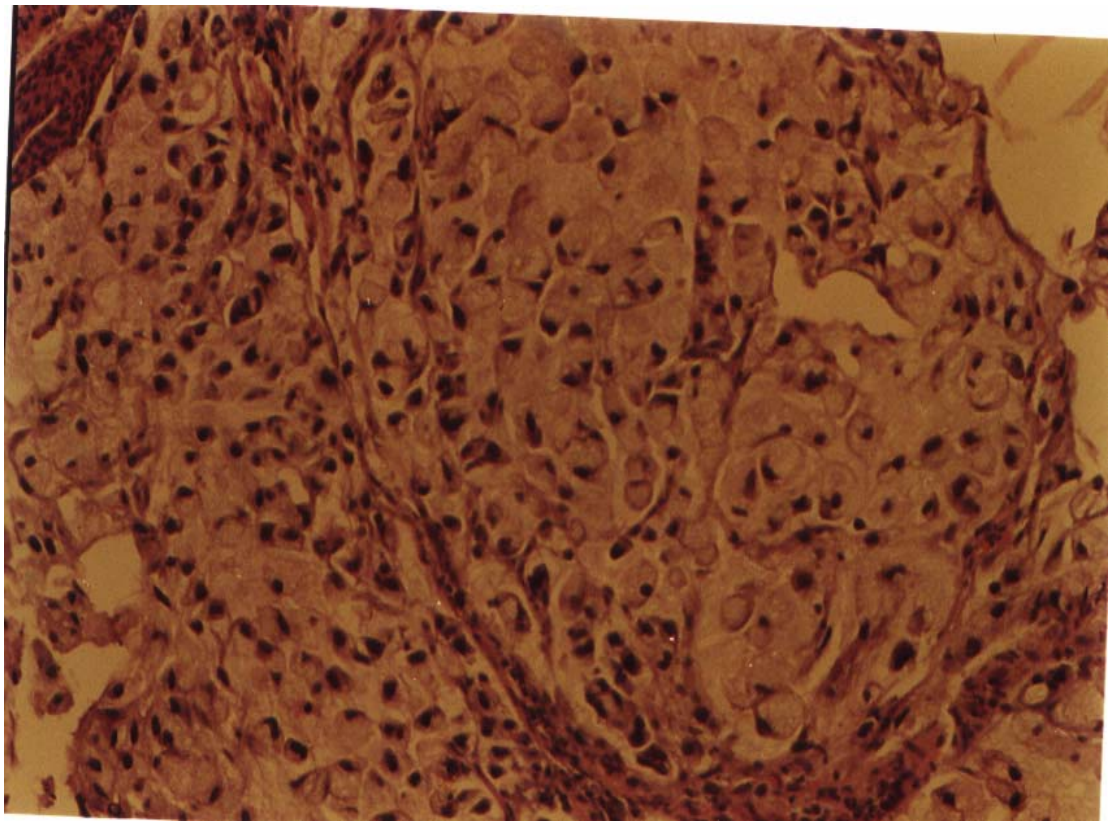
Slide (3) : Squamous intraepithelial neoplasia type III (squamous cell carcinoma in situ) (H&E X20)



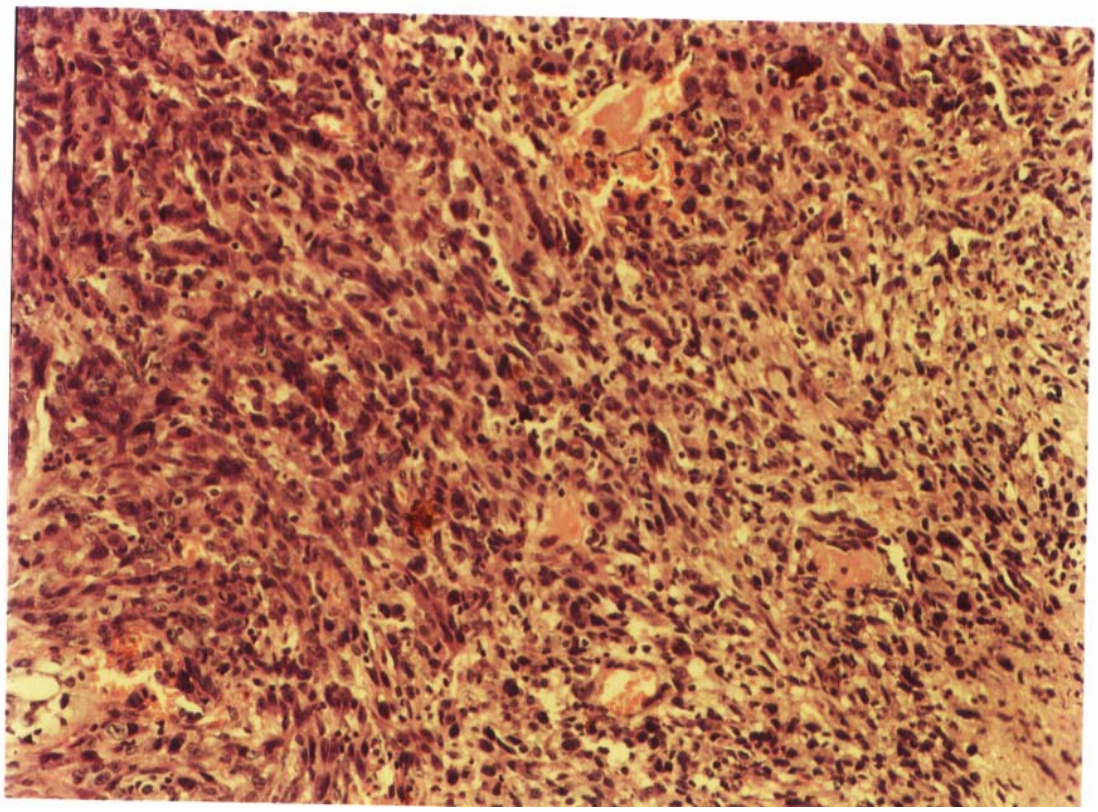
Slide (4): Moderate differentiated squamous cell carcinoma infiltrating muscle fibres (H&E X20)



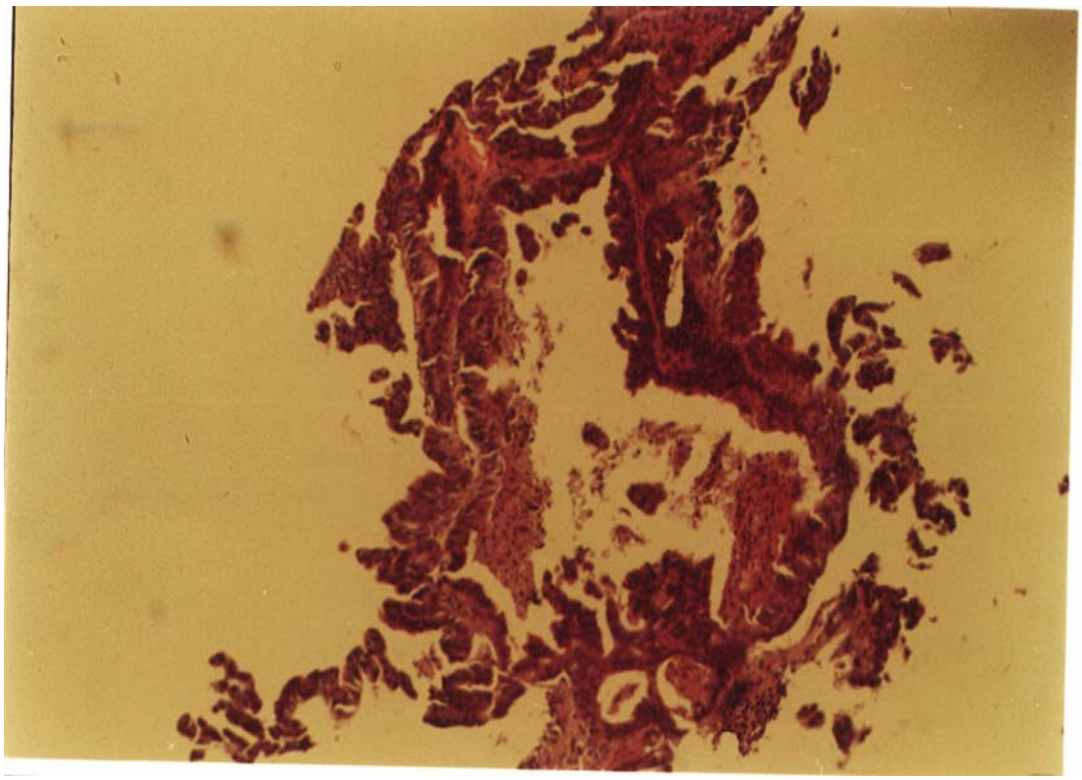
Slide (5): Basaloid squamous cell carcinoma (H&E X 10)



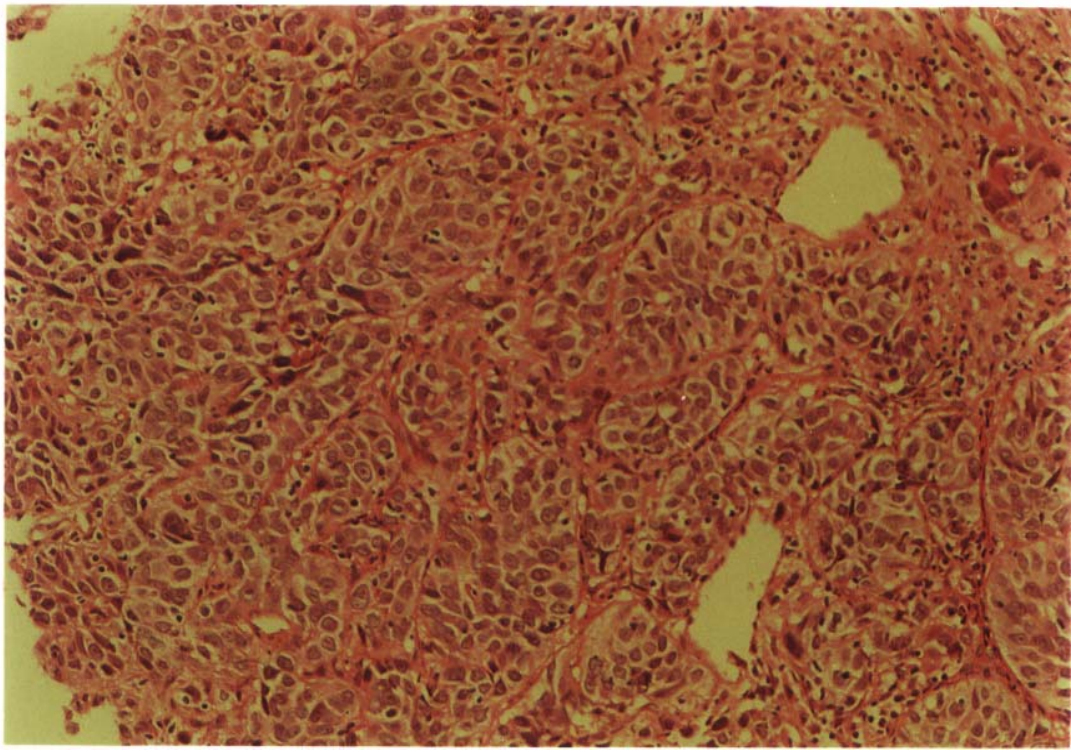
Slide (6): Signet ring carcinoma. Consisting of signet ring cells containing intracellular mucin (H&E X20)



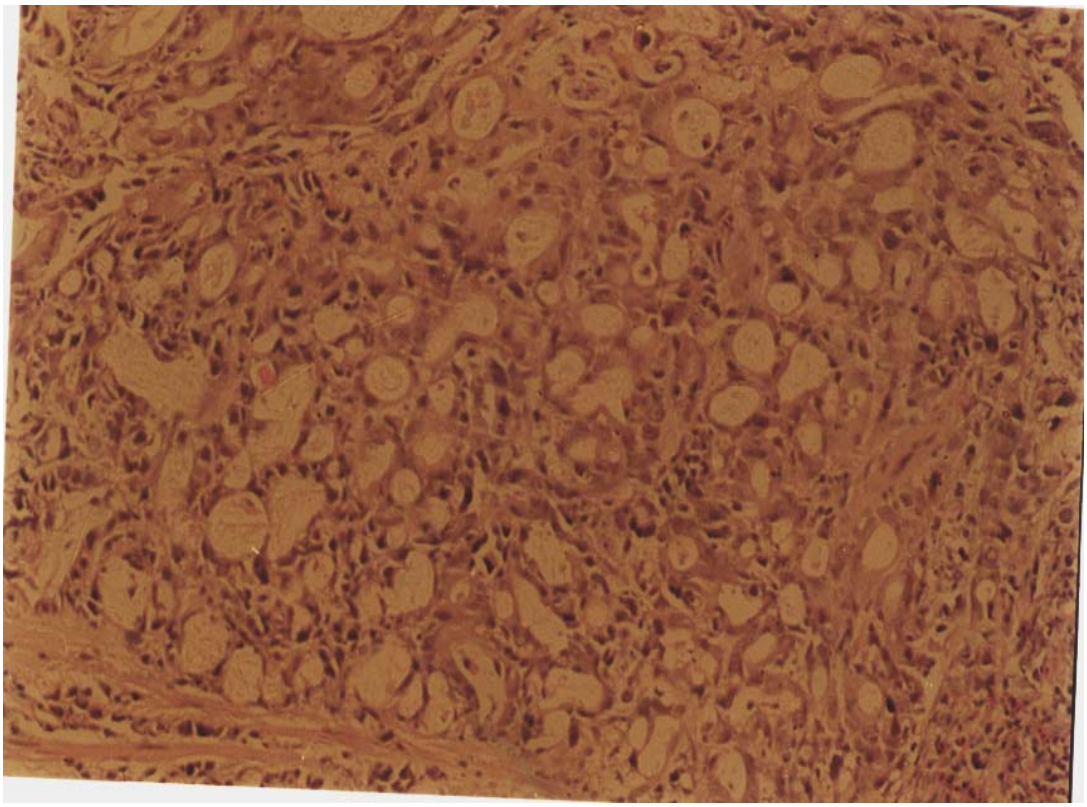
Slide (7): Spindle cell carcinoma (H&E X20)



Slide (8): Papillary adenocarcinomas (H&E X10)



Slide (9): Moderately differentiated squamous cell carcinoma (H&E X20)



Slide (10): Poorly differentiated adenocarcinoma

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